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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/650,613	08/27/2003	Vincent Geenen	ULS-001.01	8967

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EXAMINER	
EWOLDT, GERALD R	
ART UNIT	**PAPER NUMBER**
1644	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	02/02/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	10/650,613	GEENEN, VINCENT	
	Examiner	Art Unit	
	G. R. Ewoldt, Ph.D.	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *04 December 2006*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *11,13 and 16-26* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *11,13,and 16-26* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. Applicant's amendment and remarks filed 12/04/06 are acknowledged.

2. Claims 11, 13, 16-19, and newly added Claims 20-26 are being acted upon.

3. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4. Claims 11, 13, 16-19, and newly added Claims 20-26 stand/are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

As set forth previously, The instant claims encompass peptides for preventing type I diabetes and inducing tolerance in a subject at risk for developing type I diabetes. Curiously, applicant has chosen to detail some of the difficulties encountered by other researches in attempting to induce tolerance, particularly in human patients. Indeed, applicant has provided numerous references, e.g., Pozzilli, et al. (2000), demonstrating that, while the induction of tolerance would be expected, it simply does not occur. Other unsuccessful examples are known in the art. See for example, *Marketletter* (9/13/99) which teaches the complete failure of tolerance induction in human trials. Both Myloral (for multiple sclerosis) and Colloral (for rheumatoid arthritis) provided successful results in inducing tolerance in animal models, however, both were complete failures in human trials. Also note an additional more recent reference (Goodnow, 2001), wherein the author flatly states, "Obtaining the desired response [tolerance] with these strategies [tolerance induction] is unpredictable because many of these signals [tolerogenic] have both tolerogenic and immunogenic roles," (see the Abstract). The author goes on to teach that while the induction of oral tolerance might be considered "an attractive notion", the method has failed in humans because of the lack of understanding of the mechanisms involved (page 2120, column 2).

A review of the instant specification shows no induction of tolerance and indeed, it is unclear precisely what the single example is intended to demonstrate. It appears that an *in vitro* CD4 response in $DQ8^+$ diabetics to a single IGF-2 peptide was measured. Somehow, the induction of the secretion of IL-10 *in vitro* is intended to support the induction of *in vivo* tolerance with the essentially unlimited number of peptides and proteins that might be encompassed by

the instant claims.

Also note that Claim 11 would encompass fragments as small as two amino acids. Clearly then, the brief teachings of the instant disclosure, wherein no *in vivo* nor even relevant *in vitro* data is disclosed, cannot be considered to be enabling for the products of the instant claims.

In re Wands, 858 F.2d at 737, 8 USPQ2d at 1404 (Fed. Cir. 1988) indicates that the more unpredictable an area is, the more specific enablement is necessary in order to satisfy the statute. Thus, in view of the quantity of experimentation necessary, the lack of sufficient guidance in the specification, the lack of sufficient working examples, i.e., the specification discloses no data relevant to the induction of tolerance, the unpredictability of the art, and the breadth of the claims, it would take undue trials and errors to practice the claimed invention.

Applicant's arguments, filed 12/04/06, have been fully considered but they are not persuasive. Applicant argues that in view of the amendment of Claim 11 the instant rejection should be withdrawn.

While it is noted that the intended use of the claimed peptides has been amended from protecting from type 1 diabetes to restoring tolerance to islet β cells, or reducing an immune response against islet β cells, said intended use is not enabled for essentially the reasons set forth above. Indeed, as an initial matter, the intended use of the claimed peptides has actually been broadened to encompass curing (restoring tolerance) type 1 diabetes. The specification discloses no data, nor even a plausible mechanism, for said use.

As set forth previously, the specification simply fails to show, or even properly theorize, how the multitude of peptides encompassed by the instant claims could restore tolerance to islet β cells, or reduce an immune response against islet β cells. As set forth in *Rasmusson v. SmithKline Beecham Corp.*, 75 USPQ2d 1297, 1302 (CAFC 2005) the court stated:

> "As we have explained, we have required a greater measure of proof, and for good reason. If mere plausibility were the test for enablement under section 112, applicants could obtain patent rights to "inventions" consisting of little more than respectable guesses as to the likelihood of their success. When one of the guesses later proved true, the "inventor" would be rewarded the spoils instead of the party who demonstrated that the method actually worked. That scenario is not consistent with the statutory requirement that the inventor enable an invention rather

than merely proposing an unproved hypothesis."

Clearly then, the disclosure of the instant specification has not met the required standard for enablement.

5. Claims 11, 13, 16-19, and newly added Claims 20-26 stand/are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor, at the time the application was filed, had possession of the claimed invention.

As set forth previously, There is insufficient written description to show that Applicant was in possession of an IGF-2 peptide capable of preventing type I diabetes or inducing tolerance [now restoring tolerance or reducing an immune response] in a subject.

Regarding the claimed peptide, said peptide is described by function, but no common structure has been disclosed. Just a single example is disclosed, and it is unclear if it has the required functional properties. Given the breadth of the claims, it is likely, that the claimed genus of peptides is intended to be quite large. Given the lack of sufficient examples of IGF-2 peptides capable of preventing diabetes of inducing tolerance [now restoring tolerance or reducing an immune response], it is the Examiner's position that one of skill in the art would conclude that the specification fails to disclose a representative number of species to describe the peptide of the claims. See *Eli Lilly*, 119 F.3d 1559, 43 USPQ2d 1398.

Applicant does not argue this rejection separately. Accordingly, as set forth in the rejection, as *no* peptides demonstrating the claimed functionality have been disclosed the rejection is proper and has been maintained.

6. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

7. Claims 11, 13, 16, 20-22, and 25 stand/are rejected under 35 U.S.C. 102(b) as being clearly anticipated by the Sigma Catalog (1994).

As set forth previously, The Sigma Catalog teaches a human IGF-2 peptide of at least 50 amino acids suitable for vaccine use (see particularly page 1502).

Applicant's arguments, filed 12/04/06 have been fully considered but they are not persuasive. Applicant argues that the peptide of the Sigma Catalog does not comprise a pharmaceutically acceptable carrier.

A review of the reference shows that the peptide is less than 100% pure but is sterile and ready for biological use, i.e., tissue culture. The specification at page 26 discloses that the claimed peptide can be administered in solid or powder form. Accordingly, the additional reagents in the peptide of the reference can be considered to be the carrier and the peptide is ready for administration as sold. Alternatively, the manufacturer's product information sheet teaches that the peptide is to be reconstituted in balanced salt (e.g., phosphate buffer solution) and BSA (serum albumin). Accordingly, new Claim 22 has been added to the rejection. Additionally, the available package contains 10 ug which can be considered the "unit dose" of Claim 20 or 21. Additionally, given that the term "pharmaceutically active compound" is not defined in the specification, the BSA of the reconstituted peptide can be considered a "pharmaceutically active compound". Accordingly, new Claim 25 has been added to the rejection.

8. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

9. Claims 17 and 18 are rejected under 35 U.S.C. 103(a) as being unpatentable over the Sigma Catalog (1994) in view of U.S. Patent No. 6,277,375.

As set forth previously, The Sigma Catalog has been discussed above.

The reference teaching differs from the claimed invention only in that it does not teach an IGF-2 peptide of at least 75 or at least 100 amino acids.

The '375 patent teaches that the addition of an Ig Fc region to a protein can increase said protein's stability and half-life (see particularly, column 4, lines 28-37 and column 12, lines 52-59).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to add an Ig Fc region to the peptide of the Sigma Catalog to increase its stability and half-life as taught by the '375 patent.

Applicant's arguments, filed 12/04/06 have been fully considered but they are not persuasive. Applicant argues a lack of motivation to combine the references.

Adequate motivation to combine the references is set forth in the rejection.

10. Claim 19 is rejected under 35 U.S.C. 103(a) as being unpatentable over the Sigma Catalog (1994) in view of U.S. Patent No. 6,287,588.

As set forth previously, The Sigma Catalog has been discussed above.

The reference teaching differs from the claimed invention only in that it does not teach a PEGylated IGF-2 peptide.

The '588 patent teaches that PEGylation can increase a peptide's stability (see particularly, column 10, lines 57-66).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to PEGylate the peptide of the Sigma Catalog to increase its stability as taught by the '588 patent.

Applicant's arguments, filed 12/04/06 have been fully considered but they are not persuasive. Applicant argues a lack of motivation to combine the references.

Adequate motivation to combine the references is set forth in the rejection.

11. The following are new grounds for rejection necessitated by Applicant's amendment.

12. Claims 11, 13, 16-19, and newly added Claims 20-26 are rejected under 35 U.S.C. 112, first paragraph, as the specification does not contain a written description of the claimed invention, in that the disclosure does not reasonably convey to one skilled in the relevant art that the inventor(s) had possession of the claimed invention at the time the application was filed. This is a new matter rejection.

The specification and the claims as originally filed do not provide support for the invention as now claimed, specifically:

A) a composition for restoring tolerance to islet beta cells in a subject or reducing an immune response against islet beta cells in a subject comprising an IGF-2 peptide... (Claim 11)

B) a composition comprising a unit dose of about 0.07 ug to about 2800 ug (Claim 20).

C) a composition comprising a unit dose of about 0.7 ug to about 2100 ug (Claim 21).

D) a composition comprising an additional pharmaceutically active compound (Claim 25).

E) a composition comprising IL-10, TGF-β, or derivatives thereof.

Regarding A), Applicant cites pages 11 and 15. The cites, however, teach only inducing or restoring tolerance in a subject at risk for or suffering from type 1 diabetes or inhibiting or downregulating an autoimmune response.

Regarding B) and C), Applicant cites page 21. The cite does not teach the claimed ranges of unit dose.

Regarding D) and E), Applicant cites page 21. The cites teaches only an additional pharmaceutically active compound known to modulate immune responses; IL-10, TGF-β, or derivatives thereof are not disclosed.

13. Claim 26 is rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor, at the time the application was filed, had possession of the claimed invention.

There is insufficient written description to show that Applicant was in possession of "derivatives" of IL-10 or TGF-β.

None of the derivatives of the claim are described in the specification. Additionally, no common function nor structure is disclosed. Accordingly, it is the Examiner's position that one of skill in the art would conclude that the specification fails to disclose a representative number of species to describe the "derivatives" of the claims. See *Eli Lilly*, 119 F.3d 1559, 43 USPQ2d 1398.

14. Claims 23 and 24 are rejected under 35 U.S.C. 103(a) as being unpatentable over the Sigma Catalog (1994) in view of U.S. Patent No. 5,962,419.

The Sigma Catalog has been discussed above.

The reference teaching differs from the claimed invention only in that it does not teach the addition of an antioxidant to the composition.

The '419 patent teaches that peptide pharmaceutical compositions routinely include antioxidants such as ascorbic acid and EDTA (see particularly, Formulations of Pharmaceutical Compositions).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to add an antioxidant such as ascorbic acid or EDTA to the peptide of the Sigma Catalog to reduce its oxidation and increase its stability, as taught by the '419 patent.

15. Claims 25 and 26 are rejected under 35 U.S.C. 103(a) as being unpatentable over the Sigma Catalog (1994) in view of U.S. Patent No. 5,827,513.

The Sigma Catalog has been discussed above.

The reference teaching differs from the claimed invention only in that it does not teach the addition of a pharmaceutically active compound such as IL-10 to the composition.

The '513 patent teaches that IL-10 is used to treat diabetes(see particularly, the Title and Claim 1).

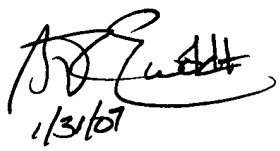
It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to add IL-10 to the peptide of the Sigma Catalog to produce a composition for treating diabetes, i.e., the loss of islet β cells, given the teachings of the '513 patent that IL-10 was already in use for the treatment of diabetes.

16. No claim is allowed.

17. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL.** See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 C.F.R. 1.136(a).

18. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Dr. Gerald Ewoldt whose telephone number is (571)272-0843. The examiner can normally be reached Monday through Thursday from 7:30 am to 5:30 pm. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (571) 272-0841.

19. **Please Note**: Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197.



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